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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,246	02/27/2004	Jeffrey David Bettencourt	03-862-B	9463

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EXAMINER	
CORDERO GARCIA, MARCELA M	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/789,246	BETTENCOURT ET AL.	
	Examiner	Art Unit	
	Marcela M. Cordero Garcia	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,10,11,17 and 25-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,10,11,17 and 25-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-5, 10, 11, 17 and 25-28 are pending in the application.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/25/07 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-5, 10-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is rendered vague and indefinite by the phrase in lines 2-3: "comprise an ionic strength equivalent to about 50 mM to about 150 mM salt equivalent". It is not clear what to about 50 mM to about 150 mM means.

All other claims that depend directly or indirectly from rejected claims and are, therefore, also rejected under USC 112, second paragraph for the reasons set forth above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 10-11 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Newton et al. (Molecular Biotechnology, January 2002) in view of

Sporeno et al. (Cytokine, 1994) and Gaberc-Porekar et al. (J Biochem Biophys Methods, 2001).

Newton et al. teach a method for purifying a 6x histidine-tagged protein (e.g., page 65, section 3.1.d, and pages 67-69, sections 3.4 to 3.8) from a protein preparation (page 65, section 3.7), comprising:

(a) concentrating the tagged protein preparation with a negatively charged capture support, wherein the negatively charged capture support comprises heparin (page 68, section 3.8.1), comprising the steps of:

(i) contacting the protein preparation with the capture support (page 68, section 3.8.1);

(ii) washing the capture support with a capture support washing buffer of low ionic strength to remove interfering molecules but not the tagged protein from the capture support (page 68, section 3.8.2); and

(iii) eluting the tagged protein from the capture support with a capture support eluting buffer of high ionic strength; (page 68, section 3.8.3);

(b) purifying the tagged protein from the eluate of step (a) (iii) with a tag-specific affinity support, wherein the tag-specific affinity support comprises nickel nitrilotriacetic acid, comprising the steps of:

(i) contacting the eluate of step (a) (iii) with the tag-specific affinity support (page 68, section 3.8.1.2);

(ii) washing the affinity support with affinity support washing buffer of low ionic strength to remove some impurities but not the tagged protein from the affinity support (page 69, section 3.8.1.4); and

(iii) eluting the tagged protein from the affinity support with an affinity support eluting buffer (page 69, section 3.8.1.5).

The limitation of claim 2: --wherein the capture support washing buffer and the affinity support washing buffer comprise an ionic strength equivalent to about 50 mM to 150 mM salt equivalent reads upon Newton et al. page 74, Note 45, which teaches a low ionic strength 20mM Tris-HCl buffer, pH 7.5, containing 10% glycerol to wash the capture support (page 68, Section 3.8 and sub-section 2) [see 112 2nd rejection above]. The limitation of claim 3: --wherein the capture support eluting buffer comprises an ionic strength equivalent to at least about 500 mM—is taught, e.g., at page 68, Section 2.8, sub-section 3, which teaches 0-1.0 M NaCl gradient in the elution buffer. The limitation of claim 4: --wherein the capture support is applied to a column before or after contacting with the protein preparation—is taught, e.g., in page 68, Section 3.8, sub-section 1 and in page 73, Note 44, lines 1-6. The limitation of claim 5: --wherein the affinity support is applied to a column before or after contacting with the eluate of the capture support-- (e.g., page 68, Section 3.8.1, sub-sections 2-4). The limitation of claim 10: --wherein the affinity support eluting buffer comprises at least 50 mM imidazole-- is taught, e.g., in page 69, Section 3.8.1, sub-section 5). The limitations of claim 17: --washing the capture support with a capture support washing buffer of an ionic strength equivalent to a concentration of about 50 mM to about 1 M to remove interfereing

molecules but not the polyhistidine-tagged cytokine from the capture support—and – washing the affinity support with affinity support washing buffer of an ionic strength equivalent to a concentration of about 50 mM to about 1 M to remove some impurities but not the polyhistidine-tagged cytokine from the affinity support-- read upon Newton et al. which teach a low ionic strength 20mM Tris-HCl buffer, pH 7.5, containing 10% glycerol to wash the capture support (page 68, Section 3.8 and sub-section 2; page 74, Note 45) and Newton et al. page 69, 3.8.1 subsection 4, which teach 20mM Tris-HCL buffer pH 7.5 containing 10% glycerol and 0.8 mM imidazole to wash the affinity support, especially in the absence of a definition of "about". Additionally, Newton et al. teach that Ni^{2+}-NTA agarose affinity column should not be the first column used in the purification procedure because of the interference of contaminating proteins (e.g., Note 44 in page 73).

Newton et al. do not teach expressly purifying a 6x histidine tagged cytokine with a four-helix bundle.

Sporeno et al. teach a method of purifying a 6x histidine tagged cytokine (page 257, column 2, lines 17-22) with a four-helix bundle motif (e.g., page 255, column 2, lines with chelating Sepharose column charged with Ni^{2+} [i.e., a tag-specific affinity support column] from a protein preparation (e.g., abstract; page 261, column 1, lines 6-10).

Gaberc-Porekar teaches that efficient purification of recombinant proteins can be accomplished with engineered histidine affinity handles attached to the N- or C-terminus, especially in combination with the Ni^{2+}-NTA matrix, which selectively binds

adjacent histidines. Since numerous neighboring histidine residues are uncommon among naturally occurring proteins, such oligo-histidine affinity handles form the basis for high selectivity and efficiency, often providing over 90% purity in one step (page 336, lines 16-22).

It would have been obvious to one of ordinary skill in the art at the time theinvention was made to modify the method of Newton et al. by applying expressly to the 6x histidine tagged cytokine with a four-helix bundle motif of Sporeno et al. by adding a heparin column step previous the tag-specific affinity support column step because, as taught by Newton et al. in Note 44, page 73, Ni^{2+}-NTA agarose affinity column should not be the first column used in the purification procedure because of the interference of contaminating proteins.

The skilled artisan would have been motivated to do so because Newton et al. teach that a 2-step process using a heparin column before the metal chelating column eliminates the majority of contaminating proteins during purification of polyhistidine proteins (see Newton et al., e.g., abstract and page 73, section 44) and because Newton et al. teach Ni^{2+}-NTA agarose should not be the first column used in the purification procedure because of the interference of contaminating proteins (e.g., page 73, Note 44, last 5 lines). Obtaining a product with lesser contaminants is a clear motivation in the art. Even though Sporeno does not expressly indicate the desirability of further purification, Gaberc-Porekar et al. teach the use of oligo-histidine affinity handles in recombinant proteins form the basis for high selectivity and efficiency during separations with Ni^{2-}-NTA affinity columns, often providing over 90% purity in one step

(page 336, lines 16-22). Please note that about 90% purity would still allow for further purification. There would have been reasonable expectation of success, given that both proteins were obtained from bacterial cells, were tagged with histidine, and could be purified via metal chelating columns (i.e., tag-specific affinity support columns). The adjustment of particular conventional working conditions (e.g., adding an extra separation processes, optimizing the ionic strength of buffers used within such purification method) is deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan. As such, it would have been obvious to one skilled in the art at the time of invention to determine all optimum and operable conditions (e.g., selection of column separation steps, optimization of buffer ionic strength for washing/elution), because such conditions are art-recognized result-effective variables that are routinely determined and optimized in the art through routine experimentation ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.". In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2145.05). One would have been motivated to determine all optimum and operable conditions in order to achieve the highest yield of the highest purity product in the most efficient manner. One would have had a reasonable expectation for success because such modifications are routinely determined and optimized in the art through routine experimentation.

From the teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed

invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 1, 17 and 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Newton et al. (Molecular Biotechnology, January 2002) in view of Sporeno et al. (Cytokine, 1994), Gaberc-Porekar et (Jkljpjpjpjpjp Biochem Biophys Methods, 2001), Lovenberg et al. (US 6,239,268) and Soussi-Gounni et al. (Molecular mechanisms in allergy and clinical immunology, 2001).

Newton et al., Sporeno et al., Gaberc-Porekar et al. are relied upon as above.

Lovenberg et al. teach human (column 2, lines 8-9) cytokines (e.g., column 1, lines 18-20) which are polyhistidine tagged, may comprise IL-9R and are purified on a NTA nickel chelating column (e.g., column 5, lines 27-49).

Soussi-Gounni et al. teach that IL-9 may play a prominent role in asthma pathology (e.g., abstract). IL-9 is a member of the 4-helix bundle cytokine family (page 575, line 12), human cytokine IL9RA gene and human IL-9R□ gene product is a protein composed of 522 amino acids (e.g., page 576, column 1, lines 9-24). Soussi et al. also teach that IL9RA may be involved in down-regulating IL-9R function. (page 576, column 1, lines 30-34).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to separate recombinant human cytokines such as those of Soussi et al. by tagging with polyhistidine as taught by Lovenberg et al., Newton et al. and

Sporeno et al. The skilled artisan would have been motivated to do so to obtain a purified product, e.g., to study the role of IL9RA in asthma. Obtaining a product with lesser contaminants is a clear motivation in the art. Even though Sporeno et al. and Lovenberg et al. do not expressly indicate the desirability of further purification, Gaberc-Porekar et al. teach the use of oligo-histidine affinity handles in recombinant proteins form the basis for high selectivity and efficiency during separations with Ni^{2-}-NTA affinity columns, often providing over 90% purity in one step (page 336, lines 16-22). Please note that about 90% purity would still allow for further purification. There would have been reasonable expectation of success, given that the various type proteins of Sporeno et al. Lovenberg et al., Newton et al. and Gaberc-Porekar were recombinantly-produced, tagged with histidine, and could be purified via metal chelating columns (i.e., tag-specific affinity support columns), including those with 4-helix bundles. The adjustment of particular conventional working conditions (e.g., electing human cytokine IL9RA within such separation method) is deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan. As such, it would have been obvious to one skilled in the art at the time of invention to determine all optimum and operable conditions (e.g., protein to be purified), because such conditions are art-recognized result-effective variables that are routinely determined and optimized in the art through routine experimentation ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.". In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2145.05). One would have been motivated to

determine all optimum and operable conditions in order to achieve the highest yield of the highest purity product in the most efficient manner in order to, e.g., study the role of IL9RA in allergic asthma. One would have had a reasonable expectation for success because such modifications are routinely determined and optimized in the art through routine experimentation.

From the teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary s-kill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicants' arguments

As indicated in the Example 1, the claimed method is surprisingly useful for the purification of minute quantities of human cytokines, providing near 100% capture for the polyhistidine-tagged cytokine and greater than 99% final purity as judged by silver stain SDS gels. Neither Sporeno et al. nor Newton et al. teach or suggest such levels of yield and purity or that such levels can be achieved by the presently claimed method.

Response to arguments

Applicant's arguments filed 9/25/07 have been fully considered but they are not persuasive for the reasons set forth above and because Gaberc-Porekar teaches that efficient purification of recombinant proteins can be accomplished with engineered

histidine affinity handles attached to the N- or C-terminus, especially in combination with the Ni^{2+}-NTA matrix, which selectively binds adjacent histidines. Since numerous neighboring histidine residues are uncommon among naturally occurring proteins, such oligo-histidine affinity handles form the basis for high selectivity and efficiency, often providing over 90% purity in one step (page 336, lines 16-22). Therefore, it would not be unexpected that adding an extra step (heparin separation) would cause a higher purity product. In addition, the limitations "minute quantities" and "nearly 100% capture and greater than 99% purity" are not included in the instant claims. Moreover, Example 1 is drawn exclusively to IL9ra, and, since claims 1 and 17 are drawn to cytokines in general, or cytokines with 4-helix bundles, the evidence provided is not commensurate in scope with the claims.

Conclusion

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcela M. Cordero Garcia whose telephone number is (571) 272-2939. The examiner can normally be reached on M-Th 7:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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MMCG 12/07

/Cecilia Tsang/
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